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(54) Title: STEREOISOMERS OF FATTY ACID ANALOGS FOR DIAGNOSTIC IMAGING

(57) Abstract

The present invention provides novel imaging agents for clinical diagnosis of injuries and diseases, in the form of a radionuclide in spatial proximity to a substantially pure stereoisomer of a fatty acid analog. The invention also provides methods for using the novel imaging agents, and kits containing one or more of the novel imaging agents of the invention.

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STEREOISOMERS OF FATTY ACID ANALOGS FOR DIAGNOSTIC IMAGING

This invention was made with Government support from the National Institutes of Health. The Government has certain rights in the invention.

The present invention relates to the field of nuclear medicine. More specifically, the invention relates to diagnostic imaging using substantially pure stereoisomers of radionuclide-containing fatty acid analogs.

BACKGROUND OF THE INVENTION

Clinical imaging technology plays a significant role in diagnosis of injuries and disease processes. Virtually any part of an animal's body can now be examined for diagnostic purposes using a variety of imaging techniques. Radiography has long been used to image body parts through which externally generated x-rays are transmitted. Computerized axial tomography (CAT) provides cross-sectional x-ray images of a plane of the body. Specific tissues or organs may be targeted in positron emission tomography (PET), single photon emission computed tomography (SPECT), and scintigraphy. In PET, SPECT, and scintigraphy, radiopharmaceutical agents capable of sequestering to some degree in the target tissue or organ are internally administered to the patient, and images are generated by detecting the radioactive emissions from the sequestered radiopharmaceutical agent. Radiopharmaceutical agents include nuclides such as ^{201}Tl, ^{99m}Tc, ^{133}Xe, and the like; chelates of nuclides; nuclide labeled metabolic agents such as ^{11}C-deoxy-D-glucose, ^{18}F-2-fluorodeoxy-D-glucose, [1-^{11}C]- and [^{123}I]-β-methyl fatty acid analogs, ^{13}N-ammonia, and the like; infarct avid agents such as ^{99m}Tc-tetracycline, ^{99m}Tc-pyrophosphate, ^{203}Hg-mercurials, ^{67}Ga-citrate, and the like; and nuclide labeled monoclonal antibodies. Whole cells such as erythrocytes and leukocytes may also be labeled with a radionuclide and function as radiopharmaceutical agents.

The amount and type of clinical information that can be derived from PET, SPECT, and scintigraphic images is related in part to the ability of the radiopharmaceutical agent to sequester in the target tissue or organ. Although many radiopharmaceuticals are available for clinical use, for a given imaging instrument, the agents generally have limitations in the resolution of the image generated. The resolution available for a particular imaging agent is highly dependent on the affinity of the radiopharmaceutical to bind at the site of injury as compared to the affinity of the radiopharmaceutical to bind to healthy tissue surrounding the site of injury.

In spite of their limitations, radiopharmaceuticals are used in a variety of types of studies to obtain different kinds of information. For example, radiopharmaceutical agents used in cardiac blood flow and blood pool studies provide information on murmurs, cyanotic heart disease, and ischemic heart disease. Perfusion scintigraphy agents provide measurements of blood flow useful in detection of coronary artery disease, assessment of pathology after coronary arteriography, pre- and postoperative assessment of coronary artery disease, and detection of acute myocardial infarction. Infarct avid agents are used for "hot spot" infarct imaging. Radiopharmaceuticals which allow binding to specific cardiac receptors, while generally still in the developmental stage, may allow detection of highly specific binding in the cardiovascular system. Radionuclide-containing antibodies directed against the heavy chain of cardiac myosin have been proposed to identify zones of acute myocardial necrosis, and ^{99m}Tc-labeled low density lipoprotein may be useful to detect atheromatous lesions in their early stages after onset of endothelial damage. ^{99m}Tc-HMPO and ^{123}I-iodoamphetamines are used to study changes in brain blood flow with SPECT. Receptor-ligand interactions, glucose utilization, protein synthesis, and other physiological parameters are also studied with other radiopharmaceuticals using PET.

Radiopharmaceutical agents capable of detecting the rate and amount of metabolism are particularly important to the progress of clinical nuclear medicine, since they allow studies of the energy consumption in the various stages of disease processes. For example, cardiac metabolism can now be studied using labeled physiologic tracers and using analogs of "natural" metabolites that are transported in the same manner as the metabolite but go through only a few reactions of the metabolic pathway and are then trapped in the tissue in a chemically known form. The glucose analog [^{18}F]-2-fluoro-2-deoxy-D-glucose can be used to detect areas of altered glucose metabolism in the heart or

other target organs which may be associated with hypoxia and anoxia and thus aid in defining the extent of an ischemic injury or cardiomyopathy. Fatty acids are the main source of energy for the heart, and radiolabeled fatty acids or their close analogs have been used to study heart metabolic integrity. β-methyl-fatty acid analogs are one group of fatty acids used as metabolic tracers.

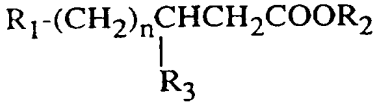
Racemic mixtures of many β-methyl-fatty acid analogs are disclosed in U.S. Pat. No. 4,524,059. One β-methyl-fatty acid analog, [^{123}I]-15-(*p*-iodophenyl)-3-R,S-methylpentadecanoic acid ([^{123}I]-BMIPP) has been used for myocardial imaging in Japan. However, the racemic nature of [^{123}I]-BMIPP makes it less than optimal for imaging studies, since uptake and metabolism of the R and S stereoisomers may differ and thus decrease the specificity of the reagent for heart tissue. Although use of stereoisomers of β-methyl-fatty acid analogs has been suggested, obtaining such isomers at a meaningful level of purity has been difficult.

Because an accurate imaging diagnosis of injury or disease depends so heavily on the agent used, a need continues to exist for radiopharmaceuticals with improved tissue and organ specificity.

SUMMARY OF THE INVENTION

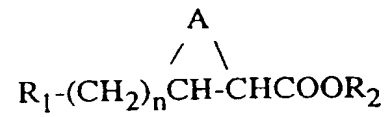
The present invention provides improved and novel radiopharmaceutical agents for diagnostic imaging of injuries and disease states. The imaging agents of the invention are radionuclide-containing analogs of fatty acids and are particularly suitable for cardiovascular and brain imaging. The imaging agents of the invention are substantially pure stereoisomers of fatty acid analogs.

In one embodiment, the invention provides an imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of more than 75% isomeric purity of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an iodoaryl group, an iodoallyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; and n is greater than 12.

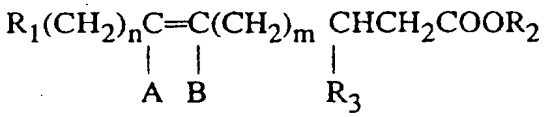
In another embodiment, the invention provides an imaging agent comprising a radionuclide in spatial proximity to an isomer of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; A is selected from the group consisting of a methylene group, an ethylene group, an oxygen, a sulfur, and a nitrogen; and n is greater than 10.

In another embodiment, the invention provides an imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of a fatty acid analog having the

formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; A is selected from the group consisting of a hydrogen, an alkyl group, and a halide; B is selected from the group consisting of a hydrogen, an alkyl group, and a halide; n is greater than 3; and m is greater than 3.

In another embodiment, the invention provides a method of imaging cardiovascular or brain tissue in a mammal which comprises administering to the mammal an imaging agent comprising a radionuclide in spatial proximity to an isomer of a fatty acid analog, and detecting the spatial distribution of the agent accumulated in the mammal.

In another embodiment, the invention provides a method of detecting a cardiovascular lesion in a mammal which comprises administering to the mammal an imaging agent comprising a radionuclide in spatial proximity to an isomer of a fatty acid analog, and detecting the spatial distribution of the agent accumulated in the mammal's cardiovascular system, wherein a detected accumulation of agent in a region which is different from the detected accumulation of agent in other regions is indicative of a lesion.

In another embodiment, the invention provides a method of detecting a brain lesion in a mammal which comprises administering to the mammal an imaging agent comprising a radionuclide in spatial proximity to an isomer of a fatty acid analog, and detecting the spatial distribution of the agent accumulated in the mammal's brain, wherein a detected accumulation of agent in a region which is different from the detected accumulation of agent in other regions is indicative of a lesion.

In another embodiment, the invention provides a kit for imaging which comprises at least one imaging agent comprising a radionuclide in spatial proximity to an isomer of

a fatty acid analog, and a pharmaceutically acceptable carrier.

In another embodiment, the invention provides a kit for imaging which comprises at least one stereoisomer of a fatty acid analog in combination with a chelating agent, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. The issued U.S. patents and allowed applications cited herein are hereby incorporated by reference.

The present invention provides imaging agents which generally comprise a radionuclide in spatial proximity to a substantially pure stereoisomer of a fatty acid analog. In accordance with the invention, spatial proximity between the nuclide and the stereoisomer may be effected in any manner which preserves the specificity of the stereoisomer for its target tissue. For example, spatial proximity between the nuclide and the stereoisomer may be effected by a covalent or non-covalent chemical bond. Such a chemical bond may be affected through a chelating substance or an auxiliary molecule. Alternatively, spatial proximity between the nuclide and the stereoisomer may be effected by incorporating the nuclide and the stereoisomer in a micelle or liposome, in such a way that the affinity of the stereoisomer for its target tissue is maintained. Spatial proximity between the nuclide and the stereoisomer may also be effected by attaching the nuclide and the stereoisomer to a matrix such as a microsphere.

As defined herein a "substantially" pure stereoisomer is one containing more than 75% of a single stereoisomer of fatty acid analog. Preferably, the substantially pure stereoisomer of the invention contains more than 75% of a single stereoisomer of a fatty acid analog. More preferably, the substantially pure stereoisomer of the invention contains more than 80% of a single stereoisomer of a fatty acid analog. Most preferably, the substantially pure stereoisomer of the invention contains more than 85% of a single stereoisomer of a fatty acid analog.

In one embodiment, the imaging agent of the invention comprises a radionuclide in spatial proximity to a stereoisomer of more than 75% isomeric purity of a β-methyl (or 2-methyl) fatty acid analog having the formula

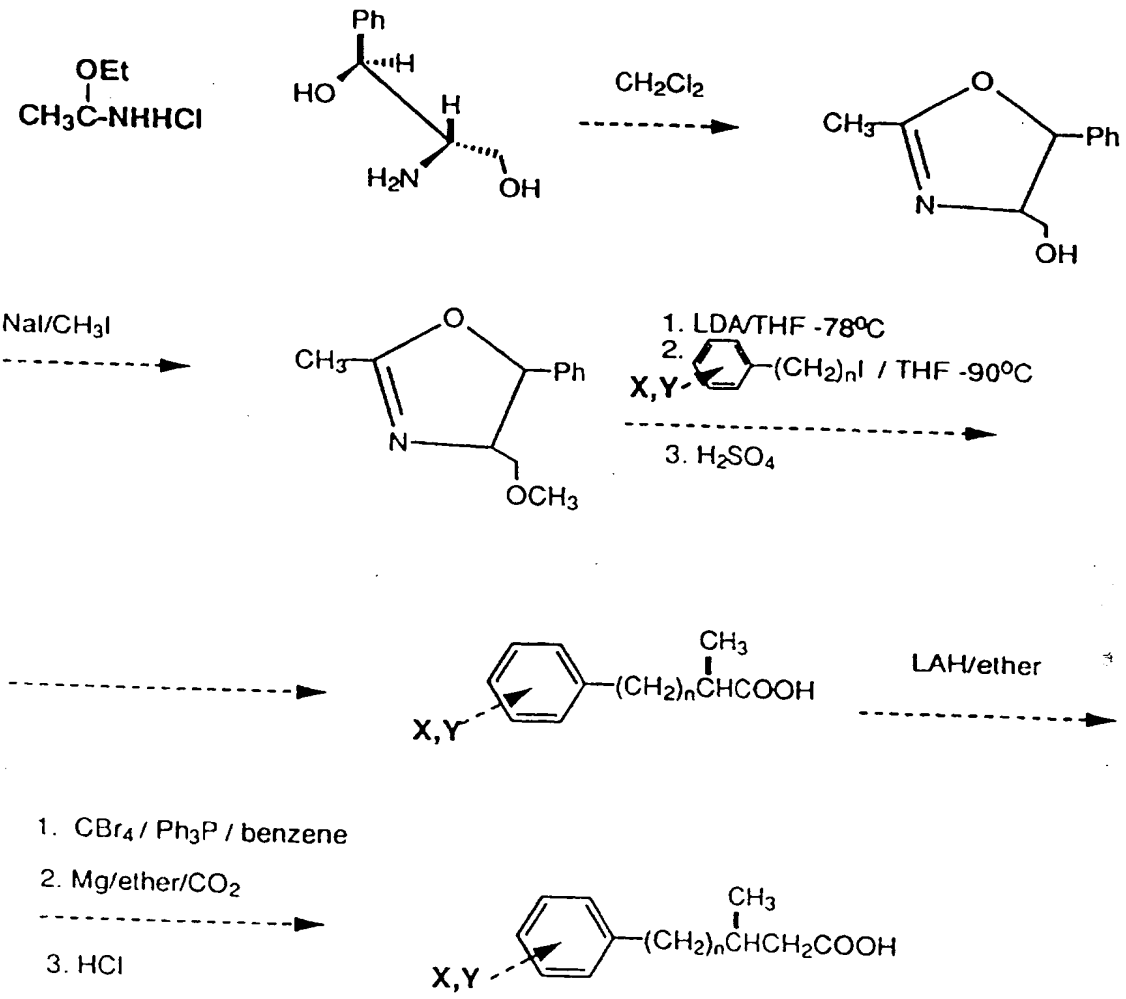
$$R_1\text{-}(CH_2)_n\,\underset{\displaystyle R_3}{\overset{\displaystyle |}{C}}HCH_2COOR_2$$

wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an iodoaryl group, an iodoallyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl

group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine and n is greater than 12. In this embodiment, the stereoisomer may be an R-stereoisomer or an S-stereoisomer. This embodiment encompasses stereoisomers having the formula as shown, where R_3 is bonded at the C3 position as shown, and in addition encompasses aliphatic fatty acid analogs having similar formulae but in which R_3 is bonded to other carbon moieties of the fatty acid chain. For example, R_3 may be bonded at the C5, C7, or C9 position of the aliphatic fatty acid chain, counting from the carboxyl carbon. Racemic mixtures of such fatty acid analogs are disclosed in U.S. Pat. No. 4,524,059.

Stereoisomers of β-methyl fatty acid analogs having greater than 75% purity as defined above may be prepared using any of the synthetic schemes set forth below. In general, the stereoisomers of the invention may be prepared using an asymmetric synthesis combined with final chromatographic separation on an optically active support or an optically active element, as indicated in Schemes 1 and 2. Alternatively, stereoisomers of the starting materials may be separated using known methods, and synthesis of the stereoisomer of the invention may be completed without changing the configuration of the optically active moiety. All precursors, intermediates, and final products of the syntheses may optionally be subjected to additional asymmetric chromatographic separations, to increase the stereoisometric purity of the fatty acid analog.

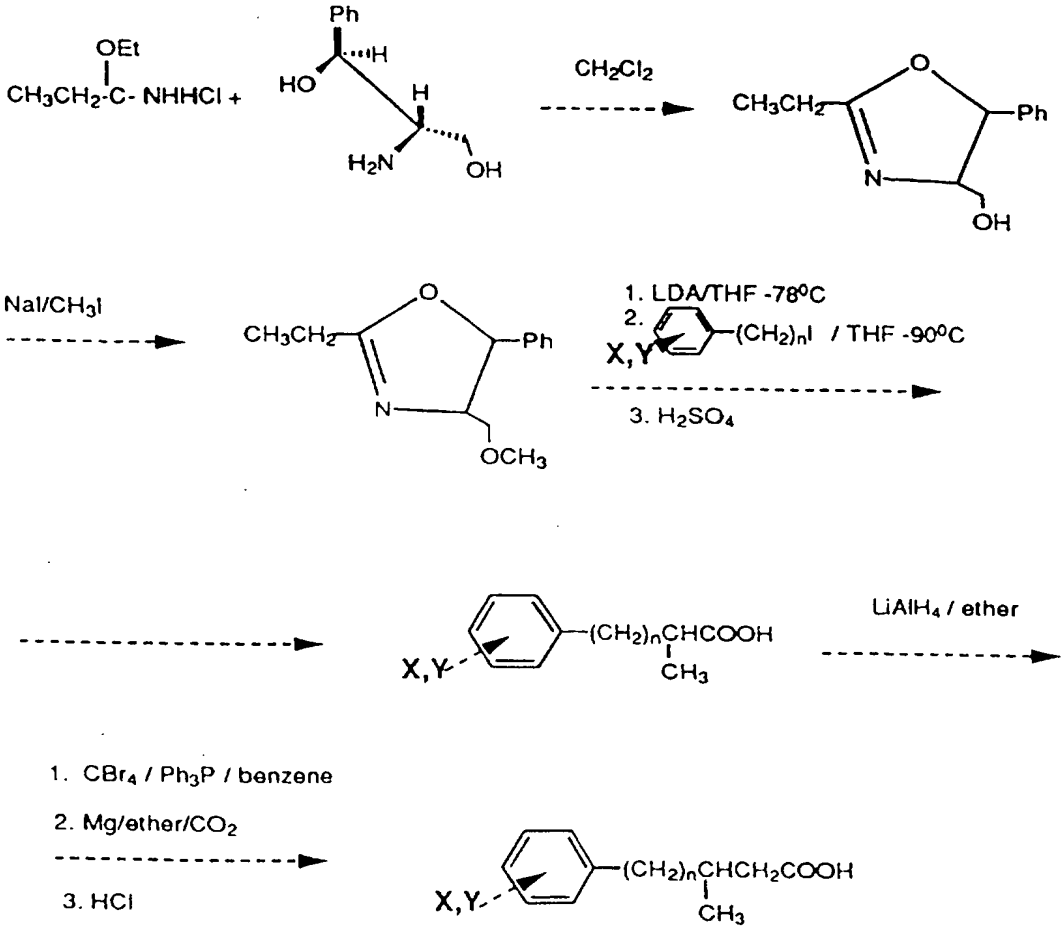
An asymetric synthesis of an R-3- methylfatty acid



X, Y = any combination of H, halogen, alkyl, aryl, acyl, alkoxy, $SnBu_3$-
diazonium-, triazine-

The final optically active product could be further enriched by asymetric chromatographic methods.

An asymetric synthesis of an S-3- methylfatty acid

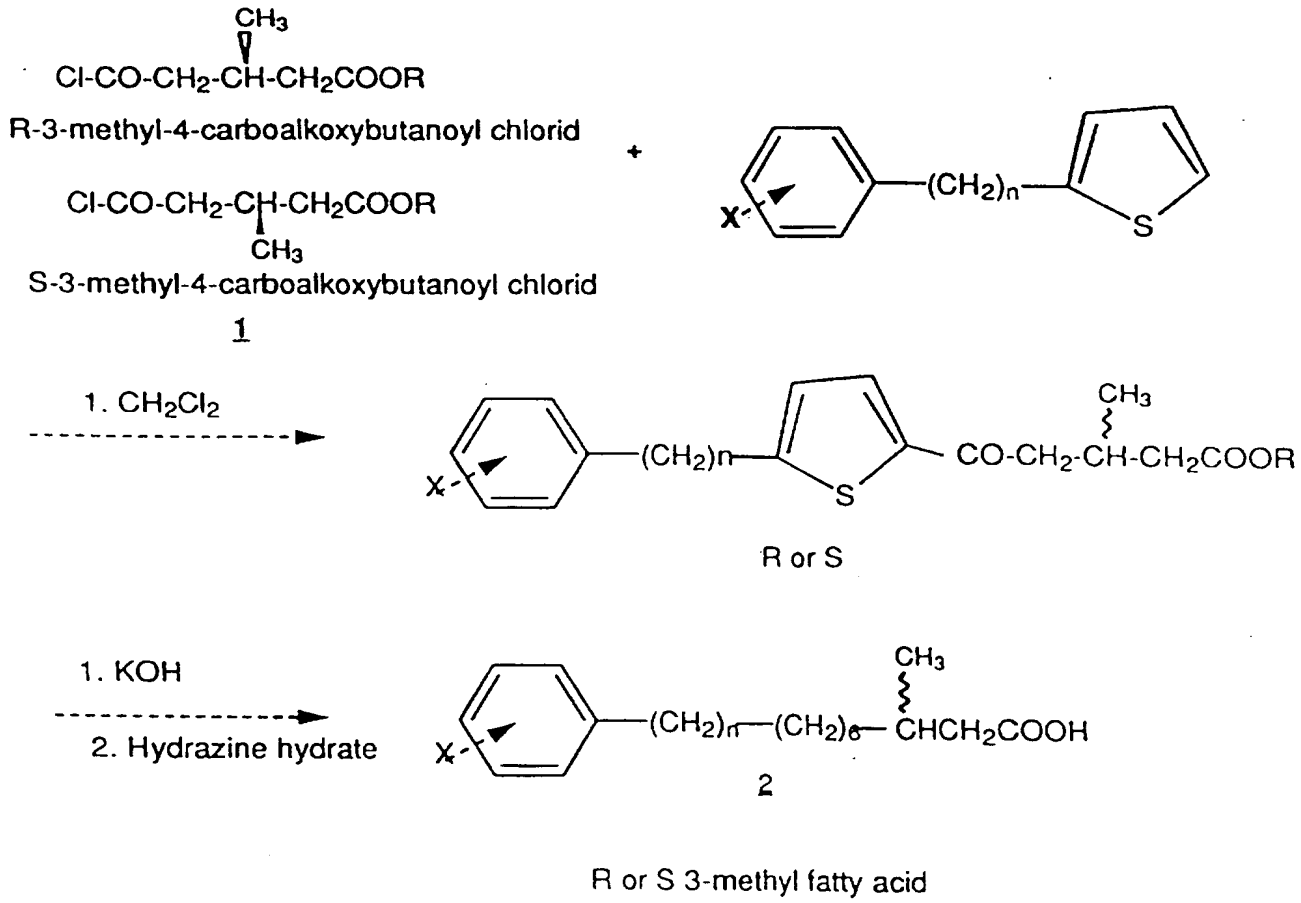


X, Y = any combination of H, halogen, alkyl, aryl, acyl, alkoxy, $SnBu_3$- diazonium-, triazine-

The final optically active product could be further enriched by asymetric chromatographic methods.

LDA = lithium diisopropyl amide THF = tetrahydrofuran

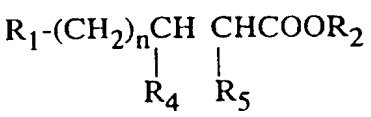
An alternative synthesis for R or S 3-methyl substituted fatty acids



X = halogen, alkyl, aryl, acyl, $SnBu_3$-, diazonium-, triazine-

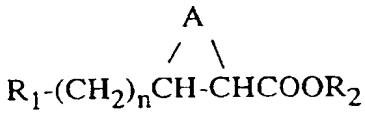
In this scheme the synthesis and separation of the optical isomers of precursor 1 is performed prior to the chemical synthesis of the final fatty acid 2. The optical isomers of 2 could be further enriched by asymetric chromatographic methods.

The invention is also embodied as an imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of an α, β-substituted (or 2,3-substituted) fatty acid analog having the formula



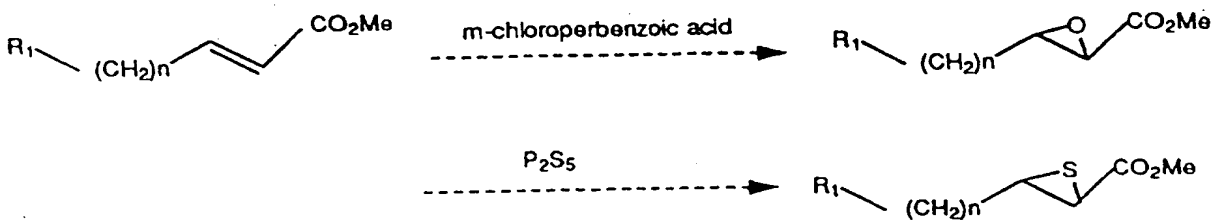
wherein R_1 is selected from the group consisting of a hydrogen, a fluorine, an iodoaryl group, an iodoallyl group and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_4 is an alkyl group; R_5 is an alkyl group; and n is greater than 12. In this embodiment, the imaging agent may be a 2S, 3S-stereoisomer, a 2S, 3R-stereoisomer, a 2R, 3R-stereoisomer, or a 2R, 3S-stereoisomer. Stereoisomers of α, β-substituted fatty acid analogs having greater than 75% purity as defined above may be prepared using modifications of synthetic schemes 1-3, wherein a hydrogen of the α-carbon is substituted with an R_4 moiety.

The invention may also be embodied as an imaging agent comprising a radionuclide in spatial proximity to an isomer of a fatty acid analog having the formula

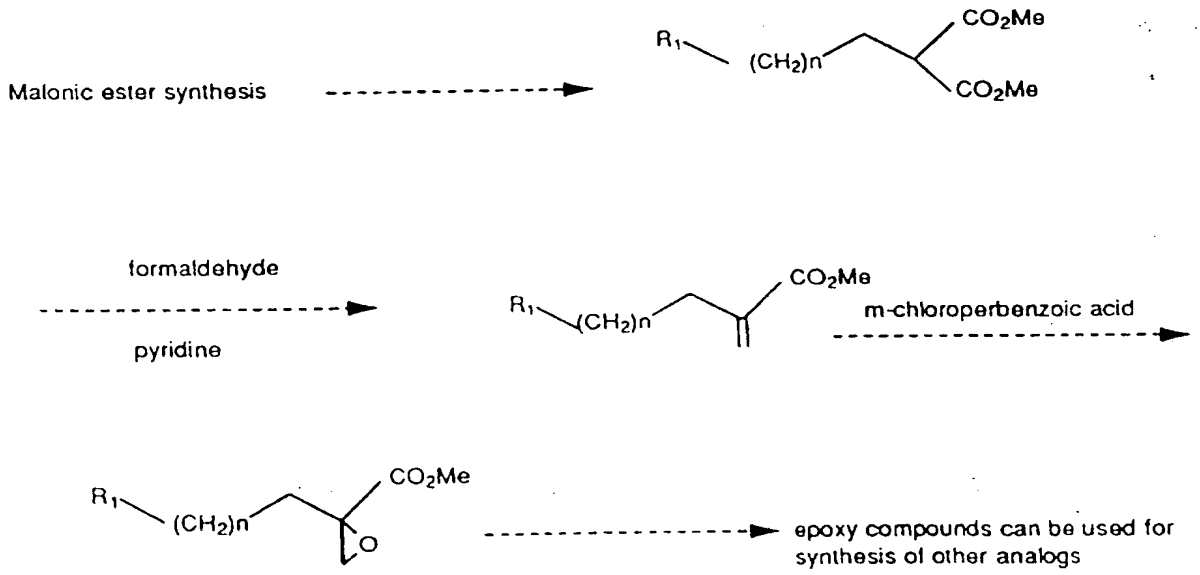


wherein R_1 is selected from the group consisting of a hydrogen, a fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; A is selected from the group consisting of a methylene group, an ethylene group, an oxygen, a sulfur, and a nitrogen; and n is greater than 10. The imaging agent of this embodiment may be prepared according to the synthetic scheme set forth below.

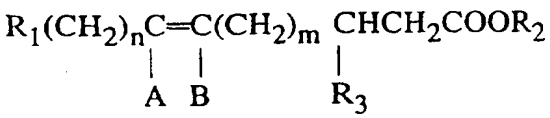
Synthesis of oxiranyl fatty acids



Alternative synthesis for betaoxiranyl fatty acids

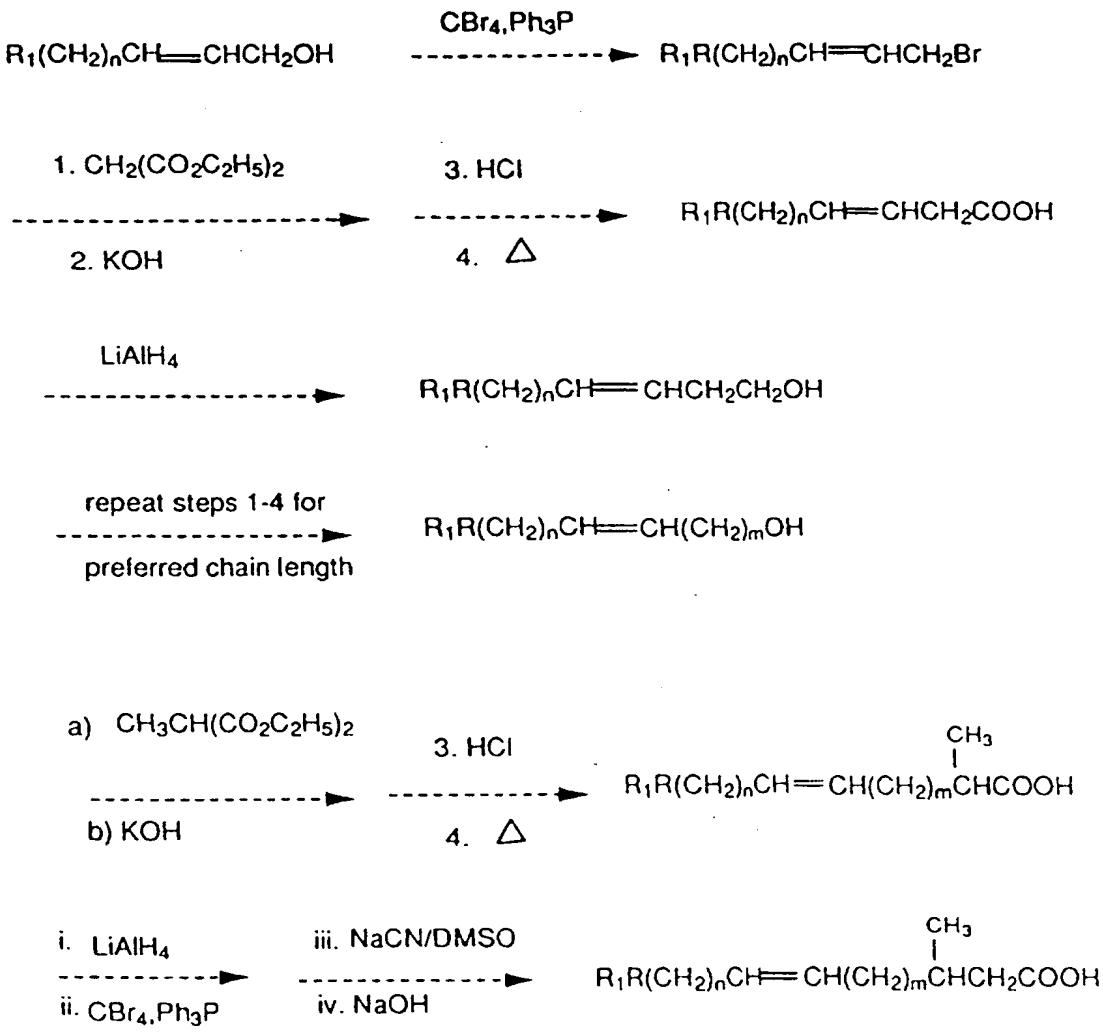


The invention is further embodied as an imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, a fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; A is selected from the group consisting of a hydrogen, an alkyl group, and a halide; B is selected from the group consisting of a hydrogen, an alkyl group, and a halide; n is greater than 3; and m is greater than 3. In this embodiment, the stereoisomer may be an R, *cis*-stereoisomer, an R, *trans*-stereoisomer, an S, *cis*-stereoisomer, or an S, *trans*-stereoisomer. Stereoisomers having greater than 75% purity as defined above may be prepared using the synthetic scheme set forth below.

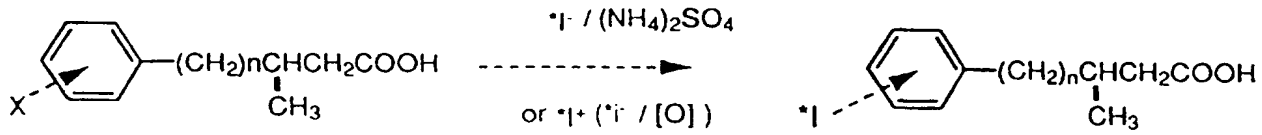
Synthesis of monounsaturated fatty acids

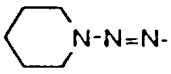


The imaging agents described above may contain any radionuclide in accordance with the invention. Preferably, the imaging agents of the invention contain radionuclides suitable for use in PET or SPECT imaging. More preferably, the imaging agent of the invention contains a radionuclide selected from the group consisting of ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga, ^{62}Cu, ^{111}In, and the like. Such radionuclides may be incorporated into the imaging agent by covalent bonding directly to an atom of the fatty acid moiety, or the radionuclide may be non-covalently or covalently associated with the fatty acid moiety through a chelating structure. Any suitable chelating structure may be used to provide the covalent or non-covalent association between the radionuclide and the fatty acid moiety of the agent. Many such chelating structures are known in the art. Preferably, the chelating structure is selected from the group consisting of an N_2S_2 structure, an N_4 structure, an isonitrile, a hydrazine, a HYNIC (hydrazinonicotinic acid) group, a phosphorus containing group, and the like. The chelating structure may be covalently or non-covalently associated with any moiety of the imaging agent. For example, the chelating structure may be associated with the R_1 moiety of the fatty acid analog, with the R_2 moiety of the fatty acid analog, or with the $(CH_2)_n$ moiety of the analog. In accordance with the invention, the stereoisomer of the fatty acid analog may be synthesized to contain a chelating group, or a chelating group may be added to the stereoisomer after synthesis.

When ^{123}I is the radionuclide, the fatty acid analog stereoisomer may be labeled in accordance with the general radioiodination protocol set forth below.

General radioiodination procedures



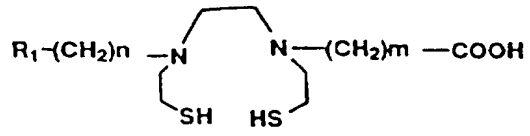
X = -$SnBu_3$;  ; I - or other groups which could be exchanged by nucleophilic or electrophilic radioioidide(ine)

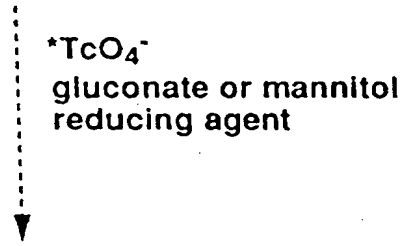
*I = $^{123,125,131}I$

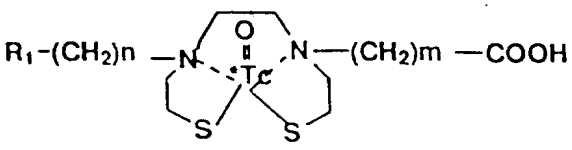
Other methods for radioiodinating the stereoisomer may also be used, for example, Bolton-Hunter radioiodination, chloramine T radioiodination, and the like.

When the radionuclide is ^{99m}Tc, the imaging agent may be labeled according to the general labeling protocol set forth below.

^{99m}Tc-radiolabeling of fatty acids





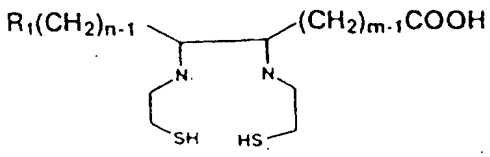


n = 2-6 : m = 2-6

R = H, halogen, alkyl, aryl, acyl, alkoxy, allyl haloallyl

*Tc = ^{99m}Tc

Other N_2S_2 fatty acid configurations are possible e.g.



The cardiovascular imaging agents of the invention may be used in accordance with the methods of the invention by those of skill in the art, *e.g.*, by specialists in nuclear medicine, to image cardiovascular or brain tissue in a mammal or to detect cardiovascular or brain lesions in a mammal. Some cardiovascular or brain lesions are evident when a dark spot appears within the image, for example, within a labeled heart or within a labeled brain, indicating the presence of necrotic tissue. Alternatively, a carcinomic lesion might be detectable as a brighter spot within the image, indicating a region of enhanced metabolism at the site of a tumor. A particularly useful imaging approach employs more than one imaging agent to perform simultaneous studies. For example, simultaneous studies of perfusion and metabolic function would allow study of coupling and uncoupling of flow and metabolism, thus facilitating determinations of tissue viability after a cardiac injury. Such determinations are useful in diagnosis of cardiac ischemia, cardiomyopathy, tissue viability, hybrinating heart, and other heart abnormalities.

The imaging agents of the invention are used in the following manner. An effective amount of the imaging agent (from 1 to 50 mCi) may be combined with a pharmaceutically acceptable carrier for use in imaging studies. In accordance with the invention, "an effective amount" of the imaging agent of the invention is defined as an amount sufficient to yield an acceptable image using equipment which is available for clinical use. An effective amount of the imaging agent of the invention may be administered in more than one injection. Effective amounts of the imaging agent of the invention will vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual and dosimetry. Effective amounts of the imaging agent of the invention will also vary according to instrument and film-related factors. Optimization of such factors is well within the level of skill in the art.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic agents, absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. The imaging agent of the invention may further be administered to an individual in an appropriate diluent or

adjuvant, co-administered with enzyme inhibitors or in an appropriate carrier such as human serum albumin or liposomes. Supplementary active compounds can also be incorporated into the imaging agent of the invention. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Adjuvants contemplated herein include resorcinols, non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether. Enzyme inhibitors include pancreatic trypsin inhibitor, diethylpyrocarbonate, and trasylol. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.* (1984) *J. Neuroimmunol.* 7, 27).

Preferably, the imaging agent of the invention is administered intravenously, and the imaging agent will be formulated as a sterile, pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred formulation for injection should contain, in addition to the cardiovascular imaging agent, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The formulation used in the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of imaging agent used for diagnostic purposes and the duration of the imaging study will depend upon the nature and severity of the condition being treated, on the nature of therapeutic treatments which the patient has undergone, and on the idiosyncratic responses of the patient. Ultimately, the attending physician will decide the amount of imaging agent to administer to each individual patient and the duration of the imaging study.

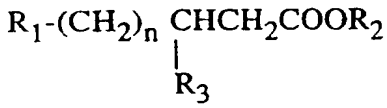
In another embodiment, the invention provides a kit for imaging which comprises one or more of the imaging agents described above, in combination with a pharmaceutically acceptable solution containing a carrier such as human serum albumin or an auxiliary molecule such as mannitol or gluconate. Human serum albumin for use in the kit of the invention may be made in any way, for example, through purification of the protein from human serum or through recombinant expression of a vector containing a gene encoding human serum albumin. Other substances may also be used as carriers in

accordance with this embodiment of the invention, for example, detergents, dilute alcohols, carbohydrates, and the like. In one embodiment, a kit according to the invention may contain from about 1 to about 30 mCi of an imaging agent. In another embodiment, a kit may contain the unlabeled fatty acid stereoisomer which has been covalently or non-covalently combined with a chelating agent, and an auxiliary molecule such as mannitol, gluconate, and the like. The unlabeled fatty acid stereoisomer/chelating agent may be provided in solution or in lyophilized form. The radionuclide, for example, ^{99m}Tc from a commercially available $^{99}Mo/^{99m}Tc$ generator, is combined with the unlabeled fatty acid stereoisomer/chelating agent for a time and at a temperature sufficient to chelate the radionuclide to the fatty acid stereoisomer/chelating agent, and the imaging agent thus formed is injected into the patient. The kits of the invention may also include other components which facilitate practice of the methods of the invention. For example, buffers, syringes, film, instructions, and the like may optionally be included as components of the kits of the invention.

Although a few exemplary embodiments of this invention have been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. For example, many other chemical groups are interchangeable with the various substituted moieties without significantly altering the activity of the stereoisometric fatty acid analog for diagnostic imaging purposes. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the following claims.

What is claimed is:

1. An imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of more than 75% isomeric purity of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an iodoaryl group, an iodoallyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; and n is greater than 12.

2. The agent of claim 1, wherein the stereoisomer is an R-stereoisomer.

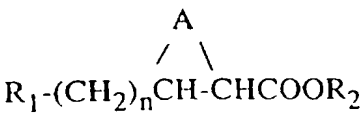
3. The agent of claim 1, wherein the stereoisomer is an S-stereoisomer.

4. The agent of claim 1, wherein the radionuclide is selected from the group consisting of ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga, ^{62}Cu, and ^{111}In.

5. The agent of claim 1, further comprising a chelating structure.

6. The agent of claim 5, wherein the chelating structure is selected from the group consisting of an N_2S_2 structure, an N_4 structure, an isonitrile, a hydrazine, a HYNIC group, and a phosphorus containing group.

7. An imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group,

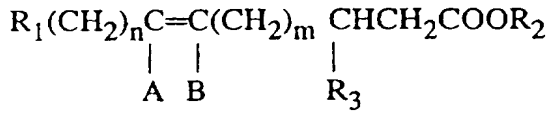
a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; A is selected from the group consisting of a methylene group, an ethylene group, an oxygen, a sulfur, and a nitrogen; and n is greater than 10.

8. The agent of claim 7, wherein the radionuclide is selected from the group consisting of ^{123}I, ^{99m}Tc, ^{18}F, ^{68}Ga, ^{62}Cu, and ^{111}In.

9. The agent of claim 7, further comprising a chelating structure.

10. The agent of claim 9, wherein the chelating structure is selected from the group consisting of an N_2S_2 structure, an N_4 structure, an isonitrile, a hydrazine, a HYNIC group, and a phosphorus containing group.

11. An imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of a fatty acid analog having the formula



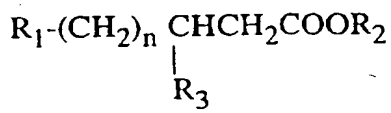
wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; A is selected from the group consisting of a hydrogen, an alkyl group and a halide; B is selected from the group consisting of a hydrogen, an alkyl group and a halide; n is greater than 3; and m is greater than 3.

12. A kit comprising the imaging agent of claim 1 and a pharmaceutically acceptable carrier.

13. A kit comprising the imaging agent of claim 7 and a pharmaceutically acceptable carrier.

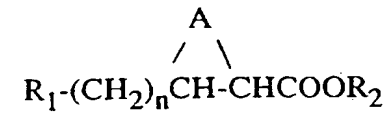
14. A kit comprising the imaging agent of claim 11 and a pharmaceutically acceptable carrier.

15. A kit comprising a stereoisomer of a fatty acid analog having the formula



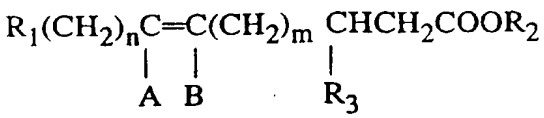
wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an iodoaryl group, an iodoallyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; and n is greater than 12, wherein the stereoisomer is combined with a chelating agent, and a pharmaceutically acceptable carrier.

16. A kit comprising a stereoisomer of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; A is selected from the group consisting of a methylene group, an ethylene group, an oxygen, a sulfur, and a nitrogen; and n is greater than 10, wherein the stereoisomer is combined with a chelating agent, and a pharmaceutically acceptable carrier.

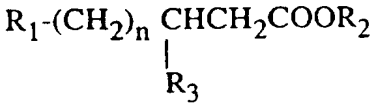
17. A kit comprising a stereoisomer of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; A is selected from the group consisting of a hydrogen, an alkyl group and a halide; B is selected from the group consisting of a hydrogen, an alkyl group and a halide; n is greater than 3; and m is greater than 3, wherein the stereoisomer is combined with a chelating agent, and a pharmaceutically acceptable carrier.

18. A method of imaging cardiovascular or brain tissue in a mammal which comprises the steps of:

a) administering to the mammal an imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of more than 75% isomeric purity of a fatty acid analog having the formula

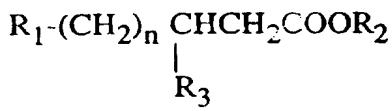


wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an iodoaryl group, an iodoallyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; and n is greater than 12; and

b) detecting the spatial distribution of the agent accumulated in the mammal.

19. A method of detecting a cardiovascular lesion in a mammal which comprises the steps of:

a) administering to the mammal an imaging agent a stereoisomer of more than 75% isomeric purity of a fatty acid analog having the formula

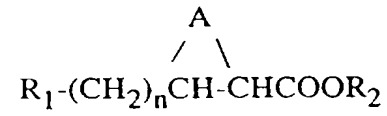


wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an iodoaryl group, an iodoallyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; and n is greater than 12; and

b) detecting the spatial distribution of the agent accumulated in the mammal's cardiovascular system, wherein a detected accumulation of agent in a region which is different from the detected accumulation of agent in other regions is indicative of a lesion.

20. A method of detecting a cardiovascular lesion in a mammal which comprises the steps of:

a) administering the mammal in imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of a fatty acid analog having the formula



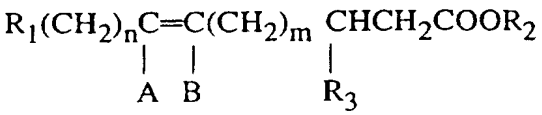
wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; A is selected from the group consisting of a methylene group, an ethylene group, an oxygen, a

sulfur, and a nitrogen; and n is greater than 10; and

b) detecting the spatial distribution of the agent accumulated in the mammal's cardiovascular system, wherein a detected accumulation of agent in a region which is different from the detected accumulation of agent in other regions is indicative of a lesion.

21. A method of detecting a cardiovascular lesion in a mammal which comprises the steps of:

a) administering to the mammal an imaging agent a stereoisomer of a fatty acid analog having the formula



wherein R_1 is selected from the group consisting of a hydrogen, fluorine, an aryl group, a substituted aryl group, an allyl group, a substituted allyl group, a vinyl group, a substituted vinyl group, and an iodothiophene group; R_2 is selected from the group consisting of a hydrogen, a primary amine, a secondary amine, a tertiary amine, an alkyl group, a substituted alkyl group, an aryl group, and a substituted aryl group; R_3 is selected from the group consisting of a hydrogen, a methyl, a hydroxyl, a keto ester, a methoxy, a halide, and an amine; A is selected from the group consisting of a hydrogen, an alkyl group and a halide; B is selected from the group consisting of a hydrogen, an alkyl group and a halide; n is greater than 3; and m is greater than 3; and

b) detecting the spatial distribution of the agent accumulated in the mammal's cardiovascular system, wherein a detected accumulation of agent in a region which is different from the detected accumulation of agent in other regions is indicative of a lesion.

22. A method of detecting a brain lesion in a mammal which comprises the steps of:

a) administering to the mammal an imaging agent comprising a radionuclide in spatial proximity to a stereoisomer of a fatty acid analog; and

b) detecting the spatial distribution of the agent accumulated in the mammal's brain, wherein a detected accumulation of agent in a region which is different from the

detected accumulation of agent in other regions is indicative of a lesion.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19024

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 51/04
US CL :424/1.11, 1.65, 1.85, 1.89

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.11, 1.65, 1.85, 1.89

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
search terms: fatty acid?, radio?, isomer?, stereoisomer?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SOLOMONS, T.W. GRAHAM. Organic Chemistry. Fourth Edition. New York: John Wiley & Sons. 1988, pages 1039-1043, see entire document.	1-22
Y	US 3,716,631 A (STEGGERDA ET AL.) 13 February 1973, column 11.	1-4
Y	US 4,473,544 A (MACHULLA ET AL.) 25 September 1984, column 3, lines 56-59 and column 5, lines 14-16.	1-22
A	US, 4,524,059 A (ELMALEH ET AL.) 18 June 1985, columns 3-6.	1-22
Y	US 4,746,505 A (JONES ET AL.) 24 May 1988, columns 5-6 and column 9, lines 56-68.	1-22

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 FEBRUARY 1997	05 MAR 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	LARA CHAPMAN KELLEY
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19024

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,370,860 A (ELGAVISH ET AL.) 06 December 1994, columns 2-5.	1-22
Y	US 4,764,358 A (KNAPP, JR. ET AL.) 16 August 1988, columns 2-5.	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19024

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-6, 12, 15, 18, 19, and 22 drawn to an imaging agent having the formula R_1-$(CH_2)_n$-$C(R_3)HCH_2COOR_2$, kits containing that imaging agent and methods of detection using that imaging agent.

Group II, claims 7-10, 13, 16, and 20 drawn to an imaging agent

having the formula R_1-$(CH_2)_n$CH-CHCOOR$_2$, kits containing that imaging agent and methods of detection using that imaging agent.

Group III, claims 11, 14, 17 and 21, drawn to $R_1(CH_2)_nC(A)=C(B)(CH_2)_mC(R_3)HCH_2COOR_2$, kits containing that imaging agent and methods of detection using that imaging agent.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The compounds which form each imaging agent have different structural formulae. The compound of Group I is linear and contains only single bonds; it lacks the special technical feature of a cyclic molecule as in Group II or a double bond as in Group III. The compound of Group II lacks the special technical feature of a linear compound as in Group I or a double bond as in Group III. The compound of Group III lacks the special technical feature of a single bonded compound as in Group I or of a cyclic compound as in Group II.